



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM:

To: Julie Breeden-Alemi, DVM

From: Kevin Ulrich, Ph.D., Entomologist

Secondary Review: Jennifer Saunders, Ph.D., Senior Biologist

Date: 4/23/2020

Subject: PRODUCT PERFORMANCE DATA EVALUATION RECORD (DER)

THIS DER DOES NOT CONTAIN CONFIDENTIAL BUSINESS INFORMATION

Note: MRIDs found to be **unacceptable** to support label claims should be removed from the data matrix.

DP barcode: 456609

Decision no.: 558585

Submission no: 1047114

Action code: R340

Product Name: Hartz Reference 156

EPA Reg. No or File Symbol: 2596-187

Formulation Type: Pet Collar

Ingredients statement from the label with PC codes included:

Deltamethrin 4.0% PC: 097805

Application rate(s) of product and each active ingredient (lbs. or gallons/1000 sq ft or per acre as appropriate; and g/m² or mg/cm² or mg/kg body weight as appropriate): Apply one 4% deltamethrin collar (1 collar = 31 g (a.i. = 1.24 g deltamethrin/collar)) per dog, 12 weeks of age or older. Remove 2-3 inches from collar buckle. Reapply 1 collar every 6 months.

Use Patterns: Collar is registered for dogs to kill fleas and ticks for up to 6 months. Proposed use claims include repelling fleas and ticks for up to 6 months and repelling and killing mosquitoes for up to 6 months. Collar should be replaced every 6 months. For use on dogs 12 weeks and older only.

I. Action Requested: Review MRIDs 51018801, 51018802 and 51018803 which were submitted to support repellency claims against fleas, ticks, and mosquitoes. MRIDs 51018801 and 51018802 contain study design and protocols only, but do not provide data. MRID 51018803 contains experimental data for three separate studies assessing both residual kill and repellent efficacy against fleas, ticks and mosquitoes for up to 6 months. The registrant submitted this data to support the addition of flea and tick repellency claims and mosquito kill and repellency claims to the product label.

II. Background: This product is currently registered to kill ticks and fleas for up to 6 months. For those claims, the company used a "cite-all" method referencing EPA Reg. No. 68451-1. Specifically, flea and tick kill claims were previously reviewed in MRID 48646602 (DP #396235). The Registrant has come in with an efficacy amendment to add repellent efficacy claims against fleas, ticks, and mosquitoes for up to 6 months.

III. MRID Summary:

MRID #51018801. Efficacy and Repellence of Ectoparasiticide Treatments against Ticks (*Dermacentor variabilis*, *Ixodes scapularis*, *Rhipicephalus sanguineus*), Fleas (*Ctenocephalides felis*) and Mosquitoes (*Aedes aegypti*) on Dogs - Protocol. Project Number: CG501/CV19/260, 2918. Unpublished study prepared by Clin Vet International.

This MRID is classified as **supplemental**. There are no data associated with this MRID. This MRID includes the protocol, deviations and amendments for MRID 51018803, which should have been submitted in the final report with 51018803 rather than as a separate MRID.

MRID #51018802. Efficacy and Repellence of Ectoparasiticide Treatments against Ticks (*Dermacentor variabilis*, *Ixodes Scapularis*, *Rhipicephalus sanguineus*), Fleas (*Ctenocephalides felis*) and Mosquitoes (*Aedes Aegypti*) on Dogs - Timelines. Project Number: CG501/CV19/260, 2918. Unpublished study prepared by Clin Vet International.

This MRID is classified as **supplemental**. There are no data associated with this MRID. This MRID contains the study timeline which includes treatment, infestation, and assessment schedules for MRID 51018803, which should have been submitted in the final report with 51018803 rather than as a separate MRID..

MRID #51018803. Efficacy and Repellence of Ectoparasiticide Treatments against Ticks (*Dermacentor variabilis*, *Ixodes Scapularis*, *Rhipicephalus sanguineus*), Fleas (*Ctenocephalides felis*) and Mosquitoes (*Aedes Aegypti*) on Dogs - Final. Project Number: CG501/CV19/260, 2918. Unpublished study prepared by Clin Vet International.

(1) GLP

(2) Methods:

This study evaluated repellency and mortality of insecticide-treated collars for dogs containing 4% deltamethrin w/w (mean fitted collar weight = 24.32 g (a.i. = 0.97 g deltamethrin/collar)) and a placebo band against ticks (*D. variabilis*, *I. scapularis*, and *R. sanguineus*), fleas (*C. felis*), and mosquitoes (*Aedes aegypti*) for up to 6 months. Fifty-six male and female dogs aged over 6 months were used for the study. Animal weights ranged between 11.04 to 21.78 kg. No parasiticide treatments were permitted for at least 12 weeks prior to treatment or after treatment until the in-life portion of the study. Routine veterinary examinations and treatment of illness or injury were permitted during the study.

Eight individual dogs per treatment were blocked into 6 groups based on the number of live, attached ticks from the initial tick challenge performed on day -7. Group 1 animals were fitted with placebo collars (negative controls); Group 2 and 3 animals were fitted with collars (4% deltamethrin); Group 4 animals received an oral chewable tablet (NexGard, 68 mg Afoxolaner); Group 5 canines received both oral tablets and collars (4% deltamethrin); Group 6 canines were fitted with collars (3% deltamethrin). Collars were placed on dogs on day 0 according to label directions which included cutting and removing 2-3 inches of excess collar (~6.68 g). Dogs in Groups 4 and 5 received oral tablets on Days 0, 30, 60, 90, 120, 150, and 180. Separate assessment calculations and statistical analyses were completed for (1) a data set that included all dogs in the study and (2) another data set for dogs that wore the original collar fitted on Day 0 for the durations of the study (not including animals in the placebo group). For the Agency's assessment, only dogs wearing the original collar fitted on Day 0 were considered.

Ticks

Dogs were infested with *R. sanguineus* and *D. variabilis* on days 45, 92, 122, 153, 182, 185, and 211 post application of the collar. Dogs were infested with *I. scapularis* on days 52, 99, 129, 160, 189, and 192 post application of collars.

For each tick species, dogs were infested with 50 each of unfed, mixed-sex ticks and manually restrained for 15 minutes (dogs were sedated for *I. scapularis* infestations from Day 129 onwards). Ticks were initially counted at 4 hours from on-animal and in the crates (and any ticks in the crates were collected and classified), then at 24 hours for final counts, where they were counted, classified and removed (with the exception of tick challenges on Days 153, 160, 185, 192, and 211 ticks which were counted and removed 48 hours after infestation.).

Percent tick mortality for specific timepoints was determined by the following calculation:

$100 \times (M_c - M_t) / M_c$, where:

M_c = mean number of live ticks exposed to control dogs

M_t = mean number of live ticks from treated groups

Percent tick repellent efficacy (on dog) was calculated as follows:

$100 \times (M_c - M_t) / M_c$, where:

M_c = mean number of live and dead ticks collected from control dogs

M_t = mean number of live and dead ticks collected from dogs in treated groups

Percent tick repellent efficacy (in crate) was calculated as follows:

$100 \times (E_t - E_c) / E_t$, where:

E_t = mean number of live and dead ticks collected in crates of treated groups

E_c = mean number of live and dead ticks collected in crate of control group

The study sponsor reported both arithmetic and geometric means. The Agency used arithmetic means to assess efficacy. Groups were compared using a one-way ANOVA (Proc GLM, SAS) with a treatment effect on untransformed and log transformed data.

Fleas

Dogs were infested with fleas on days 62, 69, 106, 136, 160, 196, 198, 216, and 218 post application of the collar. Dogs were infested with 100 each of unfed, mixed sex *C. felis* fleas and manually restrained for 1 minute to allow fleas to disperse into the fur. Initial flea counts were performed after dogs were confined in crates for four hours after infestation. At the initial 4-hour count, any fleas found in the crates were collected and classified as live, moribund, or dead. Fleas were also recovered from the animal's fur using a comb at 4 hours. Live fleas collected from the comb 4 hours after initial challenge were re-infested on the dog. Additional flea counts and removal using a comb were completed 24 hours after infestation. For flea challenges on Days 160, 198, and 218, fleas were counted and removed 48 hours after infestation.

Percent flea mortality for specific time points was determined by the following:

$100 \times (M_c - M_t) / M_c$, where:

M_c = mean number of live fleas collected from control dogs

M_t = mean number of live fleas from treated groups

Percent flea repellent efficacy (on dog) was calculated as follows:

$100 \times (M_c - M_t) / M_c$, where:

M_c = mean number of live and dead fleas collected from control dogs

M_t = mean number of live and dead fleas collected from treated groups

Percent flea repellent efficacy (in crate) was calculated as follows:

$100 \times (E_t - E_c) / E_t$, where:

E_t = mean number of live and dead fleas collected in crates of treated groups

E_c = mean number of live and dead fleas collected in crate of control group

The study sponsor reported both arithmetic and geometric means. The Agency used arithmetic means to assess efficacy. Groups were compared using a one-way ANOVA (Proc GLM, SAS) with a treatment effect on untransformed and log transformed data.

Mosquitoes

Dogs were sedated and placed in cages with 50 each of unfed female *Ae. aegypti* on days 62, 69, 106, 136, 196, and 216 post application of the collar. Dogs were exposed to mosquitoes for one hour. After one hour, all mosquitoes were removed from the cages and determined to be alive or dead. Dead mosquitoes were checked to determine if they took a blood meal. After 24 hours, live mosquitoes were assessed for viability and for the presence of blood in their abdomen.

Percent mosquito anti-feeding efficacy was determined by the following calculation:

$100 \times (M_c - M_t) / M_c$, where:

M_c = mean number of fed mosquitoes (live and dead) exposed to control dogs

M_t = mean number of fed mosquitoes (live and dead) from treated groups

Percent mosquito mortality was calculated as follows:

$100 \times (M_c - M_t) / M_c$, where:

M_c = mean number of live mosquitoes (fed and unfed) exposed to control dogs

M_t = mean number of live mosquitoes (fed and unfed) from treated groups

Percent knockdown against live and moribund mosquitoes was calculated as follows:

$100 \times (M_c - M_t) / M_c$, where:

M_c = mean number of live and moribund mosquitoes (fed and unfed) exposed to control dogs

M_t = mean number of live and moribund mosquitoes (fed and unfed) from treated groups

The study sponsor reported both arithmetic and geometric means for each trial. The Agency used arithmetic means to assess efficacy. Groups were compared using a one-way ANOVA (Proc GLM, SAS) with a treatment effect on untransformed and log transformed data.

(3) Results:

Animals in Groups 2 and 3 were treated with the insecticide dosages identical to the subject product. Therefore, only data from Groups 2 and 3 will be evaluated against the negative control (Group 1).

Ticks

R. sanguineus

Mortality for *R. sanguineus* at 24 or 48 hours after initial infestation for any timepoint did not reach 90%. Repellent efficacy based on live and dead tick counts on dogs did not reach 70% for any timepoint. Repellent efficacy based on live and dead tick counts from crates was $\geq 90\%$ on Days 92 and 182 for both Groups 2 and 3 (Table 1). *R. sanguineus* retention at 24 hours in the control group ranged from 53.8 to 72.0%.

D. variabilis

Mortality above 90% for *D. variabilis* was achieved at 24 hours only at the Day 45 timepoint in Group 2. Mortality at 24 or 48 hours after initial infestation at any other timepoint did not reach 90%. Repellent efficacy based on live and dead tick counts on dogs did not reach 90% for any timepoints except at Day 45 for Group 2. Repellent efficacy based on live and dead tick counts from crates did not surpass $\geq 90\%$ for either Groups 2 or 3 (Table 1). *D. variabilis* retention at 24 hours in the control group ranged from 43.0 to 77.2%.

I. scapularis

Mortality for *I. scapularis* reached 90% at 24 hours after initial infestation for all timepoints. Repellent efficacy based on live and dead tick counts on dogs exceeded 90% for all timepoints except Group 2 at Day 52 (86.1%). Repellent efficacy based on live and dead tick counts from crates did not surpass $\geq 90\%$ for either Groups 2 or 3 (Table 1). *I. scapularis* retention at 24 hours in the control group ranged from 13.2 to 26.8%. Only the control groups at Day 190 had mean retention above 25%.

Table 1. Tick efficacy 24 hours after challenge

Species	Day	% Mortality		% Repellency (dog collected)		% Repellency (crate collected)	
		Group 2	Group 3	Group 2	Group 3	Group 2	Group 3
<i>R. sanguineus</i>	45	75.8	64.8	39.3	43.0	87.8	87.8
	92	51.7	59.6	44.9	53.6	96.3	95.3
	122	49.7	50.0	35.8	38.8	71.4	71.4
	182	37.3	75.3	36.3	66.9	92.3	94.4
<i>D. variabilis</i>	45	97.1	83.7	95.9	78.5	57.9	49.0
	92	75.4	61.0	75.4	59.2	89.2	88.2
	122	22.4	40.7	19.9	31.0	86.7	83.5
	182	35.2	43.0	34.2	40.0	87.2	82.6
<i>I. scapularis</i>	52	91.7	97.2	86.1	94.4	61.5	65.0
	99	100	98.1	98.1	96.1	55.2	55.1
	120	100	100	98.1	100	62.3	63.8
	190	100	100	100	100	65.6	59.5

Fleas

C. felis exceeded 90% mortality at 24 after initial infestation for all timepoints in Groups 2 and 3. Repellent efficacy based on live and dead tick counts from dogs exceeded 90% for all timepoints in both treatment groups. Repellent efficacy based on live and dead tick counts from crates was $\geq 90\%$ at 24 hours for Days 62, 106, and 136. *C. felis* retention at 24 hours in the control group ranged from 65.1 to 81.4%

Mosquitoes

Anti-feeding efficacy was $\geq 90\%$ for Day 62 and 106 for Group 2 only. Group 3 efficacy did not exceed 85% for any timepoints (Table 2). The percent of fed *Ae. aegypti* from dogs in control groups ranged between 33.4–60.6%. Knockdown efficacy at 60 minutes for Group 2 was 93.9%, 100%, 57.7%, 91.2%, 75.5% on Days 62, 69, 106, 136, and 196, respectively. Knockdown efficacy at 60 minutes for Group 3 was 93.9%, 84.4%, 63.8%, 90.5%, 80.5% on Days 62, 69, 106, 136, and 196, respectively (Table 2). Mortality of *Ae. aegypti* exceeded 90% at 60 minutes only for Group 2 at Day 62. Mortality exceeded 90% at 24 hours for all timepoints in both groups (Table 2). Mortality in the control groups ranged from 2.8–98.6% at 24 hours after mosquito release. Only Days 137 and 197 had control mortality $< 10\%$. Excluding Day 62 data (2.8% control survival), average survival averaged 70%.

Table 2. Mosquito Efficacy

Species	Day	% Anti-Feeding (@24 hours)		% Mosquito Mortality (@24 hours)		% Knockdown (@60 minutes)	
		Group 2	Group 3	Group 2	Group 3	Group 2	Group 3
<i>Ae. aegypti</i>	62	96.3	73.3	100	100	93.9	93.9
	69	84.0	84.5	100	98.7	100	84.4
	106	97.3	77.4	99.6	97.9	57.5	63.8
	136	86.8	79.7	100	99.7	91.2	90.5
	196	67.1	53.8	91.5	96.1	75.5	80.5

(4) Conclusion: Supplemental

Because repelled ticks and fleas may move away from treated animals and possibly be unrecovered, repellency should be determined indirectly by counting the number of live or dead fleas and ticks (attached or unattached) on the animal plus those live or dead in the cage that are engorged compared to the control groups. This study did not supply data for arthropods that may have fed. The study authors provided only counts of live or dead ticks and fleas on the animal or in the crate (i.e., percent tick repellent efficacy (on dog)) to assess product repellency claims. In on-animal studies, dead attached ticks or blood-fed arthropods should be classified as not repelled. Additionally, it

is not clear if moribund fleas and ticks were counted as live. Moribund arthropods should be classified “live”.

Data shows that 4% deltamethrin dog collars kills *I. scapularis* for 52 to 190 days after application. Based on counts collected from dogs only, the collar may repel *I. scapularis* for 52 to 190 days after application. However, retention averaged only 17.7% at 24 hours for the infestation time points. The Agency suggests that control animals should retain 25% of ticks throughout the study. A retention of 25% was reached only on Day 190. This product was not efficacious against *R. sanguineus* or *D. variabilis*. Except on Day 45 for *D. variabilis* in Group 2, neither mortality nor repellency for either species reached the 90% threshold.

Data demonstrates that 4% deltamethrin dog collars kills *C. felis* 62 to 197 days after application. The product is efficacious 24 hours after initial infestation. However, these results do not support product use patterns. The Direction for Use state the “maximum effectiveness may not occur for 2-3 weeks after collar placement.” This MRID only provided product performance data beginning 2 months after placement. For future studies, infestations should be made immediately after product application. As noted above, fleas that take a blood meal are not considered repelled since they can still transmit agents that may cause disease. Because engorgement was not observed, product repellency cannot be confirmed.

Mosquito anti-feeding efficacy was inconsistent between timepoints and test groups. Efficacy greater than 90% was observed in Group 2 on Day 62 and 106 only. However, an average of 42.5% of the mosquitoes blood fed in control groups. To ensure insects are healthy, at least 60% of insects should take a blood meal on control animals throughout the course of the study. Furthermore, while mortality exceeded 90% for all treatment timepoints, control mortality was >10% at all timepoints except Days 137 and 197.

IV. EXECUTIVE DATA SUMMARY:

MRIDs 51018801, 51018802 and 51018803 are **supplemental**. Individually, MRID 51018803 does not support kill and repellent efficacy claims against adult fleas or ticks for 6 months. While this product does kill for *I. scapularis* for 6 months, starting at 2 months post-application, all 3 representative tick species are required for general tick claims on products. The submitted data do not support repellent efficacy claims against *Ae. aegypti*. Due to high mortality in control groups, this product only shows acceptable kill rates for *Ae. aegypti* for up to 6 months, starting 4 months after application. For all general mosquito claims, the Agency requires acceptable efficacy data against at least one species from each of the following genera: *Aedes*, *Anopheles*, and *Culex*. Repellency claims must demonstrate that arthropods both move away from the treated animals and did not blood feed. For future submissions, the registrant should include data for infestations made 24 hours post-collar application. It should be noted that 6-month efficacy cannot be achieved by combining this study with new data showing efficacy for up to 2 months. For 6-month residual claims, data must be submitted for the full 6-month timeframe.

V. LABEL RECOMMENDATIONS:

(1) Make the following changes in Direction for Use:

Remove mention of use against mosquitoes
Remove mention of use to repel ticks and fleas.

(2) The following marketing claims are acceptable: NA

(3) The following marketing claims are unacceptable:

- [Repels fleas]
- [Kills [and][&] repels fleas]
- [Repels fleas [for] [6] [six] months]
- [Kills [and][&] repels fleas for [6] [six] months]
- [Repels [and][&] kills fleas for [6] [six] months]
- [Fleas on the dog will be repelled and killed]

- Kills *Aedes Aegypti* mosquitoes for six months
- [Repels ticks]
- [Repels ticks for 6 months]
- [Repels deer ticks]
- [Repels deer ticks for 6 months]
- [Repels and kills deer ticks][for 6 months]
- [Kills and repels deer ticks] [for 6 months]
- [Kills and repels ticks][for 6 months]
- [Kills deer ticks]
- [Repels mosquitos*]/ *{*Except California}*
- [Repels mosquitos* for six [6] months] *{*Except California}*
- [Repels mosquitos* before they bite]* *{*Except California}*
- [Repels mosquitos* so they don't bite] *{*Except California}*
- [Mosquito* repelling collar] *{*Except California}*
- [Kills fleas and [&] ticks and [&] repels mosquitos* for 180 days[!]] *{*Except California}*
- [Kills fleas and [&] ticks and [&] repels mosquitos* for 6 months[!]] *{*Except California}*
- [Provides [long lasting] protection for 6 months against fleas, ticks & mosquitos*] *{*Except California}*
- [Kills fleas and [&] ticks and repels mosquitos*[for][up to] 6 months] *{*Except California}*
- [Dog collar for flea, mosquito* & tick control] *{*Except California}*
- [Flea, mosquito* & tick collar for dogs] *{*Except California}*
- [Kills fleas and [&] ticks and repels mosquitos*] *{*Except California}*
- [Kills fleas & ticks and repels mosquitos* before they bite] *{*Except California}*
- [Kills fleas & ticks before they bite]
- [6 [Six] Month flea, tick, and mosquito* protection] *{*Except California}*
- [Repels fleas and mosquitoes* [for 6 months]] *{*Except California}*
- [Repels fleas and ticks [for 6 months]]
- [Repels fleas, ticks and mosquitoes [for 6 months]]
- [Repels deer ticks and mosquitoes* [for 6 months]] *{*Except California}*
- [Repels fleas and deer ticks [for 6 months]]
- [Repels fleas, deer ticks and mosquitoes* [for 6 months]] *{*Except California}*
- [Sustainable release technology [for long lasting control for 6 months][for long lasting [flea] [flea and tick] [flea, tick and mosquito] control for 6 months]
- [Flea, tick and [&] mosquito* collar for dogs] *{*Except California}*
- *{Icon / graphic for mosquito. {*Except California}*

(4) The following MRIDs should be removed from the data matrix: **NA**

(5) Note to PM: Existing label claims for this product include kills ticks and fleas for up to 6 months. Therefore, despite low efficacy data against ticks in the current study, flea and tick kill only claims were not recommended for removal. Only label claims added as part of this amendment were evaluated.